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| EXAMINER | |
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| RIGGS II, LARRY D | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/501,933 | MENDRICK ET AL. | |
| | Examiner | Art Unit | |
| | Larry D. Riggs II | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3-5,7-10,12-17,20-22,46-49,53-56,61 and 66-69* is/are pending in the application.

4a) Of the above claim(s) *8,10,46 and 57-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,9,12-17,20-22,47-49,53-56,61 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20 July 2004, 27 February 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election without traverse of Group I, claims 1, 3-5, 7, 9, 12-17, 20-22, 47-49, 53-56, 61 and 66 in the reply filed on 15 November 2007 is acknowledged.

Claims 8, 10, 46 and 57-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 15 November 2007.

### *Status of Claims*

Claims 1, 3-5, 7-10, 12-17, 20-22, 46-49, 53-56, 61 and 66-69 are currently pending. Claims 1, 3-5, 7, 9, 12-17, 20-22, 47-49, 53-56, 61 and 66 are under consideration.

### *Specification*

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see pages 5, 7, 11 and 42. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The title of the invention is not descriptive. The current title is "Molecular Hepatotoxicology Modeling". However, claims pertaining to the elected invention are

directed to a method of predicting a toxic effect of a compound. A new title is required that is clearly indicative of the invention to which the claims are directed.

Appropriate correction is required.

### *Claim Objections*

Claim1 is objected to because of the following informalities:

Claim 1 provides "hepaotoxin" in line 4 of step (b). It is suggested that applicant replace "hepaotoxin" with hepatotoxin for grammatical correctness.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112, 1st Paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In *In re* Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

Claims 1, 3-5, 7, 9, 12-17, 20-22, 47-49, 53-56, 61 and 66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The

claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is noted that the instant specification discloses that microarray studies are prepared from frozen tissue wherein the tissue types collected are from liver, heart, kidneys, testes, and brain (pages 47-49). The data generated from the microarray are disclosed in Tables 5A-5WWW. Therefore, the data in said tables have been reasonably construed to comprise gene expression profiles from liver, heart, kidneys, testes, and brain. One of skill in the art would not know how to predictably practice the method of predicting hepatotoxicity or liver toxicity using a database from a variety of tissues without undue experimentation as discussed below.

For example, claims 1 and 9 are respectively directed to the method of predicting hepatotoxicity or liver toxicity. The methods require the preparation of a gene expression profile from a liver tissue or liver cell sample exposed to a test compound. The database contains data generated from liver, heart, kidneys, testes, brain and bone marrow, harvested from rats exposed to a known toxin. The claimed methods require the comparison of the expression levels of genes from the gene expression profile to a database. Because the data in the database are from liver, heart, kidneys, testes, and brain, the method would not result in predicting a toxic condition specific to the liver, as claimed. Therefore, one of skill in the art would not know how to predictably use the claimed methods specific to hepatotoxicity or liver toxicity by comparing expression levels generated from a liver tissue or liver cell sample exposed to a test compound to

data in said database. One skilled in the art would require undue experimentation to be able to predict hepatotoxicity or liver toxicity when the comparison is performed with a database comprising expression data from various organs, such as liver, heart, kidneys, testes, and brain.

Further, it is noted that the data in Tables 5A-5WWW comprise the LDA score from the toxicity and non-toxicity groups. However, said data do not provide enabling support for the claimed method, because the specification does not disclose whether the LDA score of the two groups is derived from the comparison between expression profiles between a liver sample and organs such as heart, liver, testes, brain or bone marrow, individually or as a group. Without the disclosure that differential expression is specific to liver toxicity or hepatotoxicity, but not to other tissues, one skilled in the art would not be able to predictably practice the methods as claimed. Therefore, one skilled in the art would not know how to predictably practice the claimed methods specific for liver toxicity and hepatotoxicity without undue experimentation.

Applicants state in the specification (pages 37-38) that Tables 3-3DD comprise gene expression profiles of sequences from GenBank as listed in Table 1. Further, it is stated that Table 1 comprises identities of the metabolic pathways in which genes function, the gene names if known, and the unique cluster. It is noted that Table 1 does not comprise the identities of the metabolic pathways in which genes function for ALL the genes in Table 1. Further, Applicants do not provide any disclosure as to whether the listed genes are specific for the metabolic pathways in the liver, or if said genes function specifically in the liver that are involved in hepatotoxicity or liver toxicity. For

example, many of the SEQ ID numbers do not have data corresponding to pathways in general or corresponding to pathways that have been implicated in hepatotoxicity or liver toxicity. Therefore, one skilled in the art would not know how to predictably practice the claimed method specific for liver toxicity or hepatotoxicity without undue experimentation.

Specific to claims 20, 21, 66, said claims recite specific disease pathologies that are predicted with the claimed methods. Further, Table 2 provides comparison codes listed in Table 1 (paragraph 0186). However, Applicants do not disclose whether the comparison is performed with normal liver tissue and liver tissues having the respective liver disease pathologies. Therefore, one skilled in the art would not know how to predictably practice the claimed methods specific for liver toxicity as directed to the specific disease pathologies without undue experimentation.

It is noted that the specification discloses a method of creating Tables 5A-5WWW *i.e.*, obtaining Mean Tox, Mean Nontox, SD Tox, SD Nontox, and LDA Score data for particular known hepatotoxic compounds, and using the linear discriminate analysis score that measures the ability of each gene in the table to predict toxicity of a sample. Tables 5A-5WWW do not disclose expression levels, *per se*. The specification does not disclose further steps necessary for the comparison of experimental expression levels and statistical values from the database. Furthermore, Table 1 and Tables 5A-5WWW comprise gene GLGC IDs, the tables are over 100 pages long, and comprise GLGC IDs in random order. The specification does not provide guidance how to correlate data of Tables 5A-5WWW (*e.g.*, GLGC ID Nos.) to the data of Table 1 (SEQ

ID NO, GenBank Acc. No., *etc.*) and to what "genes" the data from Tables 5A-5WWW correspond. Even if one could correlate the data, one would not know which "any 10 GLGC ID Nos." correspond to genes. Therefore, the method of comparing raw gene expression levels, obtained by any randomly selected method of measurement, to data in tables 5A-5WWW in order to predict whether a compound is hepatotoxic, as in claims 1 and 9, or toxic, as in claim 7, is not enabled. It is well known in the art how to measure gene expression levels; and many methods/assays for doing so are well-established. However, each method will result in different kinds of data; e.g. fluorescent vs. radioactive signals vs. colorimetric, etc. Mathematical and/or statistical manipulations of the "raw" data are required in order to make meaningful comparisons between data from different experiments. This is supported by at least the prior art of both STEINER et al. (IDS ref 461: Environ. Health Perspect. (2004) vol. 112, pp. 1236-1248) and PENNIE et al. (IDS ref 377: Toxicology in vitro (2002) vol. 16, pp. 319-326). In particular, FARR et al. (IDS ref 146: Toxicol. Sci. (1999) vol. 50, pp. 1-9) teach that data need to be normalized (p. 4) and that several genes must be included in analysis to get relevant results. The instant specification teaches that the data in the Tables is the result of statistical manipulation of data from several samples for each gene (pages 47-51). In the absence of any similar mathematical manipulation of data derived from a gene expression profile derived from a "test" liver sample, one skilled in the art would not know how to compare the "test" data to data in the Tables. For example, one would not know how to compare fluorescent readings to the data in the Tables to arrive at a result that makes sense. Although the claims do not recite doing so, even if one were to

calculate averaged or normalized (for a machine or plate background) gene expression values from such fluorescent readings, a comparison of the resulting numbers to the Tables would still be meaningless in the absence of some frame of reference. Is one to compare a "raw" gene expression level to the LDA score number? What does that indicate? It is noted that no calculation of an LDA score, mean, (tox or nontox, or any other kind of mean) from the "measured" or test data is recited in the instant claims, nor is any other statistical or mathematical manipulation recited, such that one skilled in the art would be able to meaningfully compare the acquired gene expression data to that in the Tables. In the absence of such steps, it would require undue experimentation for one skilled in the art to determine how to compare acquired gene expression levels to the data in the Tables in order to predict whether a compound is hepatotoxic or toxic.

Thus, claims 1, 3-5, 7, 9, 12-17, 20-22, 47-49, 53-56, 61 and 66 are rejected due to a lack of enablement.

### *Claim Rejections - 35 USC § 112, 2nd Paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-5, 7, 9, 12-17, 20-22, 47-49, 53-56, 61 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "a method for predicting at least one toxic effect of a compound" in lines 1-2. The metes and bounds of the limitation are unclear because

the method steps do not achieve this. The claims end with a comparing step without actually predicting the toxic effect.

Claim 3 recites the limitation "said at least ten genes correspond to sequences listed in one of Tables 5A-5WWW." What does this "correspond" means? Does it mean that the genes consist of the sequences, or comprise the sequences? If the genes are homologous to the sequences, would that be corresponding also?

Claim 5 recites the limitation "substantially all the data or information in Tables 1-5" in line 2. The metes and bounds of the limitation are unclear as to how much data or information from the tables is considered as substantially all.

Claim 7 recites the limitation "two or more genes corresponding to sequences from one of Tables 5B, 5H, 5J, 5P, 5R, 5Y, 5AA, 5CC, 5EE, 5KK, 5OO, 5QQ, 5YY, 5AAA, 5CCC, 5JJJ, 5QQQ and 5WWW" in lines 4-5. What does this "correspond" means? Does it mean that the genes consist of the sequences, or comprise the sequences? If the genes are homologous to the sequences, would that be corresponding also?

Claim 7 recites the limitation "differential expression of said genes is indicative of the at least one toxic effect" in lines 5-7. What differential expression is meant here? Only a level of expression in tissues exposed to the compound is detected. The metes and bounds thereof are not clear in the context of the claim.

Claim 9 recites the limitation "differential expression of said genes is indicative of the hepatotoxicity" in lines 6-8. What differential expression is meant here? Only a level

of expression in tissues exposed to the compound is detected. The metes and bounds thereof are not clear in the context of the claim.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3-5, 7, 9, 12-17, 20-22, 47-49, 53-56, 61 and 66 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are drawn to a process of predicting a toxic effect of a compound comprising steps of a mathematical manipulation of comparing a gene expression profile to a database of values.

Since the claimed invention involves mathematical algorithm, which is a judicial exception, the following analysis of facts of this particular patent application follows the rationale suggested in the "Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility" (OG Notices: 22 November 2005, available from the US PTO website at http://www.uspto.gov/web/offices/com/sol/og/2005/week47/og200547.htm).

The Guidelines states:

> *To satisfy section 101 requirements, the claim must be for a practical application of the § 101 judicial exception, which can be identified in various ways (Guidelines, p. 19):*
>
> *- The claimed invention "transforms" an article or physical object to a different state or thing.*

*- The claimed invention otherwise produces a useful, concrete and tangible result.*

In the instant claims, there is no physical transformation by the claimed invention, thus the Examiner must determine if the instant claims produce a useful, tangible, and concrete final result.

In determining if the instant claims have a useful, tangible, and concrete final result, the Examiner must determine each standard individually. For a claim to be "useful", the claim must produce a final result that is specific, substantial and credible. For a claim to be "tangible", the claim must set forth a practical application of the invention that produces a real-world final result. For a claim to be "concrete", the process must have a final result that can be substantially repeatable or the process must substantially produce the same result again. Furthermore, the claim must recite a useful, tangible, and concrete final result in the claim itself, and the claim must be limited only to statutory embodiments. Thus if the claim is broader than the statutory embodiments of the claim, the Examiner must reject the claim as non-statutory.

Method claims 1, 3, 4, 7, 9, 12-17, 20-22, 47-49, 53-56, 61 and 66 do not produce a tangible final result. A tangible requirement requires that the claim must set forth a practical application of the questionnaire and scoring of answers, to produce a real-world result. The instant claims are drawn to a method of predicting a toxic effect of a compound. However, the last step of the claims includes comparing a gene expression profile to a values in a database or detecting a level of a gene expression profile, the result of the invention is a set of data, such as comparison of a profile to

database values, as in claim 1, or a differential expression, as in claims 7 and 9, which, in itself, are not tangible. Since the claim itself must include a useful, concrete and tangible final result, the instant claims are non-statutory.

This rejection could be overcome by amendment of the claims to recite that a specific final result of the process is outputted to a user, or by including a result that is a physical transformation. The applicants are cautioned against introduction of new matter in an amendment.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 4, 9, 22, 22, 47, 61 and 66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 87-97 of copending Application 10/357507 ("App. '507").

Although the conflicting claims are not identical, they are not patentably distinct from each other, because claims 87-97 of App. '507 encompass all elements of instant claims 60-97.

Instant claims 1 and 9 recite a method of predicting hepatotoxicity/liver toxicity of a test compound comprising steps of preparing a gene expression profile and comparing expression profile of the genes to a database comprising mean toxic and non-toxic gene expression values of genes exposed to a known hepatotoxin/liver toxin, wherein the genes are selected from Tables 5A-5WWW. Claims 3, 4, 21, 22, 47, 61 and 66 depend from claims 1 and 9.

Claims 87-96 of App. '507 recite a method of determining whether a test compound is a liver toxin comprising steps of preparing a normalized gene expression profile of at least ten genes from a liver sample exposed to a test compound and comparing expression levels of the genes to a model comprising gene expression levels of the genes from liver exposed to a known hepatotoxin, wherein the genes are selected from Tables 5A-5XX.

Claims 87-96 of App. '507 differs from the instant claims by using normalized gene expression profiles as opposed to gene expression profiles, comparing to a hepatotoxicity model (which has the elements of normalized mean expression levels)

and scoring the comparison of gene expression profile to the hepatotoxicity model of normalized mean expression levels.

Clearly, claims 87-96 of the copending App. '507 teaches predicting hepatotoxicity/liver toxicity of a test compound comprising steps of preparing a gene expression profile and comparing expression levels of the genes to a database comprising gene expression levels of the genes exposed to a known hepatotoxin/liver toxin and thus anticipates the instant claims 1, 3, 4, 9, 22, 22, 47, 61 and 66.

The examiner assumes that some genes in Tables 5A-5WWW and 5A-5XX overlap because both databases/models comprise genes expressed in liver tissue and are indicative of liver toxicity. It is noted that the retrieval of data from the tables is not a trivial task.

Therefore, applicants are invited to present evidence to the contrary, e.g., that the tables disclose different, non-overlapping, sets of genes, or to file a terminal disclaimer to overcome the provisional obviousness-type double patenting rejection.

Claims 1, 3-5, 9, 21, 22, 47, 61, and 66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 60-74, 78-93, and 97 of copending Application 11/059535 ("App. '535").

Although the conflicting claims are not identical, they are not patentably distinct from each other, because claims 60-74, 78-93, and 97 of App. '535 encompass all elements of instant claims 1, 3-5, 9, 21, 22, 47, 61, and 66.

Instant claims 1 and 9 recite a method of predicting hepatotoxicity/liver toxicity of a test compound comprising steps of preparing a gene expression profile and comparing expression profile of the genes to a database comprising mean toxic and non-toxic gene expression values of genes exposed to a known hepatotoxin/liver toxin, wherein the genes are selected from Tables 5A-5WWW. Claims 3, 4, 21, 22, 47, 61 and 66 depend from claims 1 and 9.

Claims 60-74, 78-93, and 97 of App. '535 recite a method of predicting at least one toxic effect of a compound comprising steps of preparing a gene expression profile from a liver sample exposed to a test compound and comparing the expression profile of the genes to a database comprising gene expression values of the genes from liver exposed to a known hepatotoxin, wherein the genes are selected from Tables 3-3DD.

Claims 60-74, 78-93, and 97 of App. '535 differs from the instant claims comparing the expression profile of the genes to a database comprising gene expression values of the genes from liver exposed to a known hepatotoxin, wherein the genes are selected from Tables 3-3DD instead of comparing expression levels of the genes to a database comprising mean toxic and non-toxic gene expression values of genes exposed to a known hepatotoxin/liver toxin, wherein the genes are selected from Tables 5A-5WWW.

Clearly, claims 60-74, 78-93, and 97 of App. '535 teach predicting hepatotoxicity/liver toxicity of a test compound comprising steps of preparing a gene expression profile and comparing expression levels of the genes to a database comprising mean toxic or non-toxic gene expression levels of the genes exposed to a

known hepatotoxin/liver toxin and thus anticipates the instant claims 1, 3-5, 9, 21, 22, 47, 61, and 66.

The examiner assumes that some genes in Tables 5A-5WWW and 3-3DD overlap because both databases/models comprise genes expressed in liver tissue and are indicative of liver toxicity. It is noted that the retrieval of data from the tables is not a trivial task.

Therefore, applicants are invited to present evidence to the contrary, e.g., that the tables disclose different, non-overlapping, sets of genes, or to file a terminal disclaimer to overcome the provisional obviousness-type double patenting rejection.

Claims 1, 3, 4, 7, 9, 12-17, 20-22, 47-49, 53-56, 61 and 66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7, 8, 10, 13-20 and 23-31 of copending Application 10/515373 ("App. '373").

Although the conflicting claims are not identical, they are not patentably distinct from each other, because claims 1-5, 7, 8, 10, 13-20 and 23-31 of App. '373 encompass all elements of instant claims, 1, 3, 4, 7, 9, 12-17, 20-22, 47-49, 53-56, 61 and 66.

Instant claims 1, 7 and 9 recite a method of predicting hepatotoxicity/liver toxicity or toxicity of a test compound comprising steps of preparing a gene expression profile and comparing expression profile of the genes to a database comprising mean toxic and non-toxic gene expression values of the genes exposed to a known toxin, wherein

the genes are selected from Tables 5A-5WWW. Claims 3, 4, 12-17, 20-22, 47-49, 53-56, 61 and 66 depend from claims 1, 7 and 9.

Claims 1-5, 7, 8, 10, 13-20 and 23-31 of App. '373 recite a method of determining whether a compound induces at least one toxic effect comprising steps of preparing a gene expression profile from a sample exposed to a test compound and comparing the expression profile of the genes to a database comprising information from Tables 5A-5MMMMM.

Claims 1-5, 7, 8, 10, 13-20 and 23-31 of App. '373 differs from the instant claims by not using just liver samples and comparing the gene expression profile only to mean toxic and non-toxic gene expression values but to data from Tables 5A-5MMMMM.

Clearly, claims 1-5, 7, 8, 10, 13-20 and 23-31 of App. '373 teach predicting hepatotoxicity/liver toxicity of a test compound comprising steps of preparing a gene expression profile and comparing expression levels of the genes to a database comprising mean toxic or non-toxic gene expression levels of the genes exposed to a known hepatotoxin/liver toxin and thus anticipates the instant claims 1, 3, 4, 7, 9, 12-17, 20-22, 47-49, 53-56, 61 and 66.

The examiner assumes that some genes in Tables 5-5WWW and 5A-5MMMMM overlap because both databases/models comprise genes expressed in liver tissue and are indicative of liver toxicity. It is noted that the retrieval of data from the tables is not a trivial task.

Therefore, applicants are invited to present evidence to the contrary, e.g., that the tables disclose different, non-overlapping, sets of genes, or to file a terminal disclaimer to overcome the provisional obviousness-type double patenting rejection.

Claims 1, 7 and 9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 86, 88 and 91 of copending Application 11/547759.("App. '759").

Although the conflicting claims are not identical, they are not patentably distinct from each other, because claims 86, 88 and 91 of App. '759 encompasses all elements of instant claims 1, 7 and 9.

Instant claims 1, 7 and 9 recite a method of predicting hepatotoxicity/liver toxicity or toxicity of a test compound comprising steps of preparing a gene expression profile and comparing expression profile of the genes to a database comprising mean toxic and non-toxic gene expression values of the genes exposed to a known toxin, wherein the genes are selected from Tables 5A-5WWW.

Claims 86, 88 and 91 of App. '759 recites a method of predicting at least one toxic effect of a test compound comprising steps of preparing a gene expression profile from a cell or tissue/ liver cell or tissue sample, exposed to a test compound and comparing the expression profile of the genes to a database comprising information from Tables 1, 2, 5, and 6.

Claims 86, 88 and 91 of App. '759 differs from the instant claims by comparing the gene expression profile to a database comprising quantitative gene expression information and not only to mean toxic and non-toxic gene expression values.

Clearly, claims 86, 88 and 91 of App. '759 teach predicting hepatotoxicity/liver toxicity of a test compound comprising steps of preparing a gene expression profile and comparing expression levels of the genes to a database comprising mean toxic or non-toxic gene expression levels of the genes exposed to a known hepatotoxin/liver toxin and thus anticipates the instant claims 1, 7 and 9.

The examiner assumes that some genes in Tables 5A-5WWW and Tables 1, 2, 5, and 6 overlap because both databases/models comprise genes expressed in liver tissue and are indicative of liver toxicity or toxicity. It is noted that the retrieval of data from the tables is not a trivial task.

Therefore, applicants are invited to present evidence to the contrary, e.g., that the tables disclose different, non-overlapping, sets of genes, or to file a terminal disclaimer to overcome the provisional obviousness-type double patenting rejection.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

## ***Conclusion***

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry D. Riggs II whose telephone number is 571-270-

3062. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LDR/
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